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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/706,738	11/12/2003	John Hilfinger	TSR-10002/38	7532
25006	7590	04/17/2006	EXAMINER	
GIFFORD, KRASS, GROH, SPRINKLE & CITKOWSKI, P.C PO BOX 7021 TROY, MI 48007-7021			SCHNIZER, RICHARD A	
			ART UNIT	PAPER NUMBER

1635

DATE MAILED: 04/17/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/706,738

Applicant(s)

HILFINGER ET AL.

Examiner

Richard Schnizer, Ph. D

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 15 February 2006.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 8-30 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 8-30 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 12 November 2003 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date <u>1/24/05</u> . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

A preliminary amendment was filed on 7/29/04. Claims 1-7 were canceled and claims 8-30 were added as requested.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 28 and 29 are rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd. v. Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-30 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-30 are indefinite because the structure of A-R₁ is unclear. Specifically, it is unclear if A-R₁ must have each of a cholesterol derivative, a C8-C-24 alkyl group, and a C8-C24 heteroatom substituted alkyl group, or whether these are intended to be recited as alternatives, because there is no conjunction (“and” or “or”) separating these claim elements.

Claims 8-19 and 30 are indefinite because it is unclear what is intended by “a secondary amine or oxygen having a nonessential N-terminal amino acid region.” First it is unclear how an oxygen, or a secondary amine, can have an N-terminal amino acid region. The phrase N-terminal implies the presence of a peptide or polypeptide, but neither a secondary amine or an oxygen is a peptide or a polypeptide. Second, it is unclear what is the meaning of “nonessential” in this context. Nonessential for what?

Claim 13 is indefinite because it requires gene delivery, but then stipulates that the delivered nucleic acid may be RNA, mRNA, miRNA, ribozyme, or antisense sequences. Although the specification defines a “gene” at page 7, lines 12 and 13 as any isolated nucleic acid of greater than 20 nucleotides, this definition would be repugnant one of skill in the art who would not consider a single stranded mRNA, miRNA, ribozyme, or antisense sequence to be a gene. A gene is a unit of heredity that encodes a transcribable product, and these molecules do not encode transcribable products.

Claims 1-30 are indefinite because the structure of A-R₁ is unclear. Specifically, it is unclear if A-R₁ must have each of a cholesterol derivative, a C8-C-24 alkyl group, and a C8-C24 heteroatom substituted alkyl group, or whether these are intended to be

recited as alternatives, because there is no conjunction (“and” or “or”) separating these claim elements.

Claims 21 and 22 are indefinite. These claims require a cholesterol derivative, defined in claim 20 as “A-R₁”, wherein A is a hydrophilic moiety that must have each of a C₀-C₄ alkylhydroxy group, a substituted amino group, a quaternary amino group, a sulfonate group, a phosphonate group, a carboxylate group, and a targeting ligand. However, none of the cholesterol derivatives (A-R₁ groups) recited in claims 21 or 22 has this combination of groups.

Claim 23 is indefinite because it recites “said A derivative” without antecedent basis. Claim 23 is also indefinite because A cannot be only “hydroxyl”. Claim 20 from which claim 23 depends, requires that A must have each of a C₀-C₄ alkylhydroxy group, a substituted amino group, a quaternary amino group, a sulfonate group, a phosphonate group, a carboxylate group, and a targeting ligand.

Claim 24 is indefinite because it recites “said Q derivative” without antecedent basis.

Claims 28 and 29 provide for the use of a bile acid salt but, since the claims do not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

Claim 30 is indefinite because it recites “a composition of Formula I according to claim 8”, but claim 8 does not recite any formula I.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

New Matter

Claims 25 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 25 is drawn to a composition as set forth in claim 20 wherein Y and Z together yield a net neutral charge. This embodiment does not appear to be supported in the specification or claims as originally filed, and so it represents new matter.

Enablement

Claims 8-19, 28-30 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 8-19 are drawn to methods of treating any disease condition or deficiency without limitation through gene delivery to target cells of a subject by administering to

any site a nucleic acid complex. Claim 13 stipulates that the nucleic acid in the complex may be selected from the group consisting of: DNA, RNA, mRNA, miRNA, ribozyme, RNase, and antisense sequences. The essence of the invention appears to be the use of a lipidic moiety such as a cholesterol derivative or alkyl group conjugated to a cationic group suitable for binding a nucleic acid. Claims 28 and 29 are included in this rejection because they could be interpreted as methods of delivering a nucleic acid to a subject in vivo. Claim 30 is drawn to a composition with an intended use of gene delivery in vivo to a subject. The only purpose disclosed in the specification for gene delivery to a subject in vivo is treatment of a disease condition or deficiency, so enablement of these claims is dependent on whether or not the specification enables treatment of a disease condition or deficiency.

The specification lists at pages 4-6 over 100 "conditions and deficiencies" that the method can be used to treat. However, it must be noted that at least 49 of the listed items are not diseases or conditions, but instead are proteins or body parts. Proteins that can be expressed according to the invention include proteases, pituitary hormones, protease inhibitors, growth factors, cytokines, somatomedins, chemokines, immunoglobulins, gonadotrophins, interleukins, chemotactins, interferons, and lipid-binding proteins, insulin, interferon-alpha2B, human growth hormone (hGH), transforming growth factor (TGF), erythropoietin (EPO), ciliary neurite transforming factor (CNTF), clotting factor VIII, insulin-like growth factor-1 (IGF-1), bovine growth hormone (BGH), granulocyte macrophage colony stimulating factor (GM-CSF), platelet derived growth factor (PDGF), interferon-alpha2A, clotting factor VIII, brain-derived

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neurite factor (BDNF), thrombopoietin (TPO), insulintropin, tissue plasminogen activator (tPA), IL-1, IL-2, urokinase, IL-1 RA, streptokinase, superoxide dismutase (SOD), adenosine deamidase, catalase, calcitonin, arginase, fibroblast growth factor (FGF) (acidic or basic), neurite growth factor (NGF), phenylalanine ammonia lyase, granulocyte colony stimulating gamma-interferon factor (G-CSF), L-asparaginase, pepsin, uricase, trypsin, chymotrypsin, elastase, carboxypeptidase, lactase, sucrase, intrinsic factor parathyroid hormone (PTH)-like hormone, calcitonin, Ob gene product, cholecystikinin (CCK), glucagon, glucagon-like-peptide I (GLP-1), and insulinotrophic hormone.

The specification provides no working example of gene therapy. It discusses dosage and administration in general terms at page 9, first paragraph, but does not specifically address the treatment of any disease or disorder in particular. Applicant envisions oral, rectal, intravenous, intramuscular, subcutaneous, intracisternal, intravaginal, intraperitoneal, intravesical, buccal, and nasal delivery. See page 15, lines 5-10. Although claim 13 explicitly recites gene therapy with miRNA, ribozyme, or antisense sequences, the specification does not disclose any such sequences.

At the time the invention was made, successful implementation of gene therapy protocols was not routinely obtainable by those skilled in the art. Verma et al (Nature 389: 239-242, 1997) taught that "there is still no single outcome that we can point to as a success story (p. 239, col 1). The authors stated further, "Thus far, the problem has been the inability to deliver genes efficiently and to obtain sustained expression" (p.239, col. 3). Anderson (Nature 392:25-30, 1998) confirmed the unpredictable state of the

art, stating that “there is still no conclusive evidence that a gene-therapy protocol has been successful in the treatment of human disease” (p. 25, col. 1) and concluding, “Several major deficiencies still exist including poor delivery systems, both viral and non-viral, and poor gene expression after genes are delivered” (p.30). More recently, Romano et al (2000) reviewed the general state of gene therapy, and found that the problems relating to gene delivery and expression discussed above persisted. See entire document, especially, last sentence of abstract; last sentence of column 1 on page 20 to column 2, line 6; page 21, column 1, lines 1-9 and 18-21; sentence bridging columns 1 and 2 on page 21; and first sentence of last paragraph on page 21. This idea was echoed by Somia and Verma (2000), who noted that delivery vehicles still represented the Achilles heel of gene therapy, and that no single vector existed that had all of the attributes of an ideal gene therapy vector. See page 91, column 1, lines 5-13 of first paragraph. Rosenberg et al (Science 287 :1751, 2000) stated that “[a]t present the ethos of the new field of gene therapy is clearly not working. Since the inception of its clinical trials a decade ago, gene therapy’s leading proponents have given the field a positive “spin” that is unusual for most medical research. Yet, despite repeated claims of benefit or even cure, no single unequivocal instance of clinical efficacy exists in the hundreds of gene therapy trials.” See first full paragraph. Juengst (BMJ 326: 1410, 2003) indicated that the effects of gene therapy on cells are often multiple and unpredictable. See title and last sentence of first full paragraph of column 2. In summary, it is clear that gene therapy is considered highly experimental area of research at this time, and researchers acknowledge that demonstrable progress to date

has fallen short of initial expectations due to inadequate delivery and expression systems, and the unpredictable and pleiotropic effects of gene insertion and/or expression.

The prior art of record is devoid of successful gene therapy methods using oral delivery. However, the prior art does teach the use of cholesterol derivatives comprising polycation moieties for gene delivery. For example, Stupp et al (US Patent 5,932,539, issued 8/1999) taught a biodegradable polymer of the general formula L- P- T wherein L is a cholesteryl moiety, P is a divalent linker, and T is a polyionic organic group such as polylysine. See claim 1, column 6, lines 25-32, and sentence bridging columns 6 and 7. Epand et al (US Patent 5,283,185, issued 2/1/94) and Mahato (US Patent 6,696,038, issued 2/2004) taught conjugates of cholesterol derivatives and polyethyleneimine for gene delivery. See Epand at abstract, claims 1 and 10, and compound XV, described at column 9, lines 45-58. See claims of Mahato. However, in view of the state of the art of gene therapy as set forth above, none of these inventions was sufficient to overcome the inability to achieve efficient gene delivery and expression that form the barriers to successful gene therapy.

In view of the unlimited breadth of disease conditions and deficiencies that are embraced by the instant claims, the state of the art and unpredictability of gene therapy in general, the failure to provide any working example of gene therapy, the failure to provide specific guidance pertaining the treatment of any specific disease or disorder, and the fact that delivery compositions of similar structure to those claimed have not been sufficient to overcome the art-recognized barriers to gene therapy, one of skill in

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the art would have to perform undue experimentation in order to practice the invention as claimed.

Conclusion

No claim is allowed. The closest prior art of record is Stupp et al (US Patent 5,932,539) who taught a biodegradable polymer of the general formula L- P- T wherein L is a cholesterolyl moiety, P is a divalent linker, and T is a polyionic organic group such as polylysine, and its use to delivery nucleic acids in vivo. See claim 1, column 6, lines 25-32, and sentence bridging columns 6 and 7. If the A-R₁ group in claim 8 had been defined as being one of a cholesterol derivative, a C₈-C₂₄ alkyl group, or a C₈-C₂₄ heteroatom substituted alkyl group, then Stupp would have anticipated claims 8, 14, 15, and 17. If A-R₁ in claim 20 had been defined as above, and the A group in claim 20 had been defined as one of, instead of all of, a C₀-C₄ alkylhydroxy group, a substituted amino group, a quaternary amino group, a sulfonate group, a phosphonate group, a carboxylate group, and a targeting ligand, then Stupp would have anticipated or rendered obvious claims 20, 24, 26-27 and 30. Claims 21-23 would have been obvious over the combination of Stupp with any one of US Patents 4,522,803, 5,026,557, or 5,254,339 which indicate that cholestanol, coprostanol, and bile acids are obvious equivalents to cholesterol groups.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Richard Schnizer, whose telephone number is 571-272-0762. The examiner can normally be reached Monday through Friday between the

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hours of 6:00 AM and 3:30. The examiner is off on alternate Fridays, but is sometimes in the office anyway.

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Andrew Wang, can be reached at (571) 272-0811. The official central fax number is 571-273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

A handwritten signature in black ink, appearing to read 'Richard Schnizer', with a stylized flourish at the end.

Richard Schnizer, Ph.D.
Primary Examiner
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S #	Updt	Database	Query	Time	Commer
<u>S23482</u>	<u>U</u>	PGPB,USPT,USOC,EPAB,JPAB,DWPI,TDBD	(5,932,539.pn.) and (nucleic or gene or polynucl\$ or oligonucle\$ or plasmid or dna)	2006- 04-14 06:59:02	
<u>S23481</u>	<u>U</u>	PGPB,USPT,USOC,EPAB,JPAB,DWPI,TDBD	mahato.in. and cholester\$	2006- 04-14 06:46:29	
<u>S23480</u>	<u>U</u>	PGPB,USPT,USOC,EPAB,JPAB,DWPI,TDBD	(4522803 or 5026557 or 5254339 or 5912340).pn. and (cholestanol or coprostanol or cholic or cholate or chenodeoxychol\$ or doxychol\$)	2006- 04-14 06:42:36	
<u>S23479</u>	<u>U</u>	PGPB,USPT,USOC,EPAB,JPAB,DWPI,TDBD	(4522803 or 5626557 or 5254339 or 5912340).pn. and (cholestanol or coprostanol or cholic or cholate or chenodeoxychol\$ or doxychol\$)	2006- 04-14 06:42:06	
<u>S23478</u>	<u>U</u>	PGPB,USPT,USOC,EPAB,JPAB,DWPI,TDBD	(5,932,539.pn.) and cholest\$	2006- 04-14 06:32:14	
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<u>S23476</u>	<u>U</u>	PGPB,USPT,USOC,EPAB,JPAB,DWPI,TDBD	(5,932,539.pn.) and cholester\$	2006- 04-14 06:31:39	
<u>S23475</u>	<u>U</u>	PGPB,USPT,USOC,EPAB,JPAB,DWPI,TDBD	5,932,539.pn.	2006-	

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		04-14 06:31:15
<u>S23474</u>	<u>U</u> PGPB,USPT,USOC,EPAB,JPAB,DWPI,TDBD 5932539.pn.	2006-04-13 15:30:30
<u>S23473</u>	<u>U</u> PGPB,USPT,USOC,EPAB,JPAB,DWPI,TDBD 20050026859.pn. and nonessential	2006-04-13 14:44:28
<u>S23472</u>	<u>U</u> PGPB,USPT,USOC,EPAB,JPAB,DWPI,TDBD 20050026859.pn.	2006-04-13 14:43:51
<u>S22806</u>	<u>U</u> PGPB,USPT,USOC,EPAB,JPAB,DWPI,TDBD 20050026859.pn. and (CHOLIC OR CHOLATE OR DEOXYCHOL\$)	2006-03-07 15:17:23
<u>S22805</u>	<u>U</u> PGPB,USPT,USOC,EPAB,JPAB,DWPI,TDBD 20050026859.pn. and neutral	2006-03-07 15:09:27
<u>S23276</u>	<u>U</u> PGPB,USPT,USOC,EPAB,JPAB,DWPI,TDBD (cholesterol same (glycochol\$ or chenodeoxychol\$ or desoxychol\$ or glycochenodeoxychol\$ or taurochol\$ or taurochenodeoxychol\$) same (hydrophobic or lipid)	2006-04-03 15:14:37
<u>S23275</u>	<u>U</u> PGPB,USPT,USOC,EPAB,JPAB,DWPI,TDBD cholesterol same (glycochol\$ or chenodeoxychol\$ or desoxychol\$ or glycochenodeoxychol\$ or taurochol\$ or taurochenodeoxychol\$)	2006-04-03 15:14:20
<u>S23274</u>	<u>U</u> PGPB,USPT,USOC,EPAB,JPAB,DWPI,TDBD cholesterol same (glycochol\$ or chenodeoxychol\$ or desoxychol\$ or glycochenodeoxychol\$)	2006-04-03 15:13:52

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or taurochol\$ or
taurochenodeoxychol\$)
same hydrophobic
same lipid\$

S23273 U PGPB,USPT,USOC,EPAB,JPAB,DWPI,TDBD cholesterol same 2006-
(cholestanol or 04-03
coprostanol or cholic or 15:08:46
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or chenodeoxychol\$ or
desoxychol\$ or
glycochenodeoxychol\$
or taurochol\$ or
taurochenodeoxychol\$)
same hydrophobic
same lipid\$

S23272 U PGPB,USPT,USOC,EPAB,JPAB,DWPI,TDBD cholesterol same 2006-
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same lipid\$

S23271 U PGPB,USPT,USOC,EPAB,JPAB,DWPI,TDBD cholesterol same 2006-
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or taurochol\$ or
taurochenodeoxychol\$)
same hydrophobic

S23270 U PGPB,USPT,USOC,EPAB,JPAB,DWPI,TDBD cholesterol same 2006-
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desoxychol\$ or
glycochenodeoxychol\$

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or taurochol\$ or
taurochenodeoxychol\$)

S23269 U PGPB,USPT,USOC,EPAB,JPAB,DWPI,TDBD 5932539.pn.

S23126 U PGPB,USPT,USOC,EPAB,JPAB,DWPI,TDBD 5932539.pn. and 2006-03-
(disulfide or 20
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or sulphur or cross
link\$)

S23125 U PGPB,USPT,USOC,EPAB,JPAB,DWPI,TDBD (cholesterol same 2006-03-
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or bifunctional or
linker)

S23124 U PGPB,USPT,USOC,EPAB,JPAB,DWPI,TDBD cholesterol same 2006-03-
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lysine or poly 14:36:51
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